fMRI Gets *BOLD*er at High Fields

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The majority of fMRI experiments are conducted based on the blood oxygenation level dependent (BOLD) contrast [1-3], which is derived from the fact that deoxyhemoglobin is paramagnetic while oxyhemoglobin, similar to tissue, is diamagnetic, and changes in the local concentration of deoxyhemoglobin in the brain lead to alterations in the MRI image intensity. It is generally accepted that neuronal activation induces an increase in regional blood flow without a commensurate increase in the regional oxygen consumption rate ($CMRO_2$) [4-6]. Consequently, local capillary and venous deoxyhemoglobin concentrations decrease during neuronal activation, leading to an increase in T_2* and T_2. This increase is reflected as an elevation of intensity in T_2*- and T_2-weighted MR images. Based on this principle, to map neuronal function, T_2* (or T_2) – weighted images are acquired consecutively while the subject either rests or performs certain task or is presented with certain stimuli. These images are subsequently analyzed with statistical methods to ascertain regions exhibiting significant signal changes between the task performance/stimulation and resting periods.

For fMRI based on the BOLD contrast, high magnetic fields are very desirable because, as discussed below, both the sensitivity and specificity increase with the magnetic field. In fact, the desire to improve the sensitivity and specificity of fMRI has been a major force driving the move towards higher and higher magnetic fields for *in vivo* MR. It is generally accepted that the signal-to-noise ratio (SNR) in MR images scales linearly with the field strength [7] and this view is experimentally demonstrated to the field strength as high as 7 T although the B1 field and hence the coil sensitivity become somewhat nonuniform at very high magnetic fields [8].

In addition to the increase in SNR, theoretical considerations indicate that the BOLD contrast increases supralinearly with the field strength, depending on contributions from static and dynamic averaging [9]. The effect of the BOLD field inhomogeneity on the MR signal has been discussed extensively by others [9, 10] and is briefly summarized here. In the brain, hemoglobin stays within blood vessels and its effect on water protons depend on the location of the protons relative to the blood vessel. For the extravascular (i.e., tissue) spins, there is the dynamic averaging effect, which arises due to diffusion during the echo time (TE). Because the diffusion distance within typical TE is rather small, dynamic averaging is prominent mainly for small blood vessels, e.g. capillaries, which are separated on the average by 50 μm [10]. Dynamic averaging leads to a change in T_2 [9], thereby the BOLD contrast in

both spin-echo and gradient-echo images. For large blood vessels, the effect of dynamic averaging for extravascular spins is negligible because diffusion distance is negligible compared with the size of these large vessels and *static averaging* is the main mechanism for the BOLD effect. Static averaging comes into play if refocusing pulses are not used or asymmetric spin echoes are acquired. The aforementioned picture of the extravascular BOLD effect was supported with numerical calculations [10, 11], which also provided quantitative assessment of the BOLD induced R_2*/ R_2 changes and its dependence on the vessel size. Dynamic averaging was found to be dominant for small vessels (diameter < 8 μm at ~4T), and static averaging for large vessels (diameter > 10μm at ~4T). While this vessel size dependence is also a function of the field strength, these calculations suggest that large vessel effects mostly arise from static averaging and small vessel contributions are dominated by dynamic averaging. Furthermore, it is useful to note that the dynamic averaging effects, mediated by diffusion, depends on the field inhomogeneity, hence the static magnetic field, quadratically while the static averaging effect depends on the static magnetic field linearly[9].

Because both the raw SNR and the BOLD contrast increase with the field strength, the sensitivity of fMRI goes up with the field strength more than quadratically, despite a shortening in transverse relaxation times (T_2 and T_2*) at high fields. This increase in sensitivity has been experimentally demonstrated at fields up to 7 T in humans [12, 13] and 9.4 T in animals[14]. When noise is taken into account, a detailed study examining the BOLD response in the motor area [15] revealed that the contrast-to-noise ratio (CNR) at 3.0 T is 1.8-2.2 times that at 1.5 T.

The increase in the sensitivity at high fields has been exploited to improve spatial resolution or temporal resolution or both [16, 17]. Studies have used 4 T magnets to elucidate the columnar organization in the visual cortex in human subjects [18, 19]. More interestingly, a recent study of the rat sematosensory cortex performed at 11.7 T [20] has revealed the ability of high field fMRI in providing a map of layer specific structure. The high sensitivity of high field fMRI has also been employed to study the temporal characteristics of the BOLD response. At 4 T, fMRI was used in one of first studies of event-related fMRI, exhibiting fMRI's ability to differentiate brain regions based their responses' temporal characteristics [21]. In a true *single* trial experiment at 4 T [22], the ability of fMRI to detect temporal information in individual trials, permitting a direct correlation with corresponding behavioral response, was demonstrated. Another interesting aspect of high-field fMRI is the detection of the initial dip [23-27], which is believed to arise from an initial increase in deoxyhemoglobin concentration before the hemodynamic response takes place and to be more specific to the site of neuronal activation than the hyperemic BOLD response. This response was also shown to increase with the magnetic field strength [27].

In addition to the increase in sensitivity, high magnetic fields also provide high specificity for fMRI. As pointed above, large vessel contributions scale linearly with the field while small vessel contributions scale quadratically with the field strength. Consequently, microvascular contributions become more pronounced at high fields due to its quadratic dependence on B_0. This improves the spatial specificity of BOLD based fMRI, because capillary contributions are closer to the site of neuronal activation while large vessels are not uniformly distributed and may be spatially distant (~ 10 mm) from the activation. While such an increase in specificity is demonstrated in T_2*-weighted fMRI data [12, 13], this increase in sensitivity becomes more dramatic in T_2-weighted fMRI images as discussed below.

In a T_2 based BOLD fMRI map, the signal changes come from 1) intravascular blood T_2 changes, from both large and small blood vessels, and 2) extravascular effect associated *only with* microvessels (capillaries and small post-capillary venules). Therefore, in T_2-weighted fMRI, only possible large vessel contribution comes from intravascular blood signal. Fortuitously, at very high fields, T_2 of the venous blood is very short [18-19], significantly attenuating the intravascular signal and hence the intravascular BOLD response. Thus, at high fields, T_2 based fMRI is mostly sensitive to microvascular contributions and more specific. In addition, the quadratic increase in the sensitivity of T_2 BOLD contrast makes it possible to perform T_2 based fMRI. In a recent study performed on human subjects at 7 T, activation patterns were found to localize to the gray matter [28]. In addition, the BOLD contrast was found to increase significantly with spatial resolution, suggesting that the partial voluming effect is significant. This point has been demonstrated by several studies at high fields ranging from 4 to 9.4 Tesla [14, 29]. A more quantitative study has also examined the point spread function of the T_2 vs. T_2* response and revealed significantly narrower response for the T_2 BOLD maps [30].

In summary, theoretical considerations and experimental data obtained so far at fields as high as 11.7 Tesla indicate that high magnetic fields provide an increase in both sensitivity and specificity. Such an increase is being exploited to improve spatial and/or temporal resolution in fMRI. In addition, this increase has also fueled the rapid expansion of high field MR.

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